Adenoid Cystic Carcinoma of the Head and Neck

Predictors of Morbidity and Mortality

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Objectives: To review 160 patients treated at a single institution for adenoid cystic carcinoma during the 20 years between 1977 and 1996, applying a consistent treatment of surgery and postoperative radiation therapy to 140 patients. To analyze factors governing treatment failure, treatment-related morbidity, and mortality.

Design: Retrospective review.

Setting: Tertiary referral center.

Patients: Seventy-seven males and 83 females aged 13 to 89 years (average age, 49.5 years).

Results and Conclusions: Combined treatment yielded an 85% locoregional freedom from relapse and disease-specific survival at 5, 10, and 15 years was 89%, 67.4%, and 39.6%, respectively. Thirty-five patients (21.9%) had distant metastases as the only site of failure. Patients treated for paranasal sinus tumor experienced the most treatment-related morbidity vs other sites. Perineural invasion of major nerves was associated with increased treatment failures. Four or more symptoms present at diagnosis, positive lymph nodes, solid histology, and peripheral invasion of major nerves were associated with increased mortality from disease.


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DENOID CYSTIC carcinoma (ACC) is a rare malignant tumor that affects major and minor salivary glands, lacrimal glands, ceruminous glands, and occasionally excretory glands of the female genital tract. Adenoid cystic carcinoma is well known for its prolonged clinical course and the tendency for delayed onset of distant metastases. The combination of surgery and postoperative radiation therapy has enabled us to improve locoregional control of disease, but the prolonged clinical course, spanning decades, has made it difficult to determine whether the treatment option affects survival. Little progress has been made in the treatment of disseminated disease, the lungs being the organ most frequently affected. When metastases occur in bone, especially the spine, the course of disease is usually fulminant.

This is a retrospective review of a single institution’s experience with ACC in which a consistent surgery and radiation treatment philosophy was applied. We report on treatment outcome, identifying the factors responsible for locoregional failure, overall survival, and the treatment-related significant morbidity as determined through chart review.

RESULTS

Disease-specific survival at 5, 7, 10, and 15 years was 89.0%, 74.8%, 67.4%, and 39.6%, respectively (Figure 1). Treatment failure was documented in 59 (36.9%) of the 160 patients. Disease-free intervals ranged from 2 months to 19 years. Eleven patients (6.9%) had local failure only; 35 patients (21.9%) had distant metastases only; 1 (0.6%) had local failure; 1 (0.6%) had only regional failure; and 11 (6.9%) had both distant failure and either local or regional failure. These results yield a locoregional control rate of 85%. The most common type of failure was distant, and the most common sites of distant failure were the lung (67% of metastases) and liver (12%). Figure 2 compares the survival of patients with isolated locoregional failure with that of patients with isolated distant failure.

Perineural invasion was documented in 79 patients; minor (unnamed) nerve involvement only was present in 43, whereas major (named) nerve inva-
PATIENTS AND METHODS

Charts of 160 patients diagnosed as having ACC of the head and neck and treated at The University of Texas M.D. Anderson Cancer Center between 1977 and 1996 were reviewed. The cohort included 77 males and 83 females, ranging in age from 13 to 89 years (average age, 49.3 years). Tumor sites are the following:

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palate</td>
<td>32</td>
</tr>
<tr>
<td>Other oral cavity, oropharynx</td>
<td>34</td>
</tr>
<tr>
<td>Paranasal sinus</td>
<td>29</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td>24</td>
</tr>
<tr>
<td>Parotid</td>
<td>18</td>
</tr>
<tr>
<td>Larynx</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
</tr>
</tbody>
</table>

All slides of tissue obtained for diagnosis were available and were reevaluated by one of us (A.E.-N.). Because of observations that solid growth architecture has prognostic implications, tumors were categorized as “solid” or “not solid” histopathological variants. To be considered solid, specimens had to fulfill 2 criteria: presence of the classic solid histological pattern for ACC in 10% of tissue examined or more, and presence of areas of anaplasia within the solid architecture.

While several primary surgeons and radiation oncologists were involved over the years, a consistent treatment philosophy was used throughout the study period, with regular multidisciplinary conference preview and approval of the treatment plan in all cases. One hundred forty patients were treated with a combination of surgery and radiotherapy, 17 with only surgery, and 3 with only radiotherapy. Instances of single-modality therapy were due to either patient preference or, in the case of surgery, satisfactory control of very limited disease.

The Table shows the variables on which data were gathered for the following analyses: treatment failure, morbidity, and survival. Treatment failure was defined as recurrence of tumor, determined clinically or pathologically. Morbidity, sequelae of therapy, and quality of life after treatment were assessed by thorough review of reports of complications in the patients’ medical records. We characterized morbidity as “none/mild” or “moderate/severe.” Among those reporting morbidity, we recorded the number requiring major therapy. Survival was defined as disease-specific survival. Median follow-up time for failure analysis was 78 months (range, 2-237 months). Minimum follow-up for survival analysis was 5 years, or until the time of death. Survival statistics were calculated at 5, 7, 10, and 15 years.

Different categories of patient data were compared by χ² analysis, and when the number of observations in a given group dropped below 6, by the Fisher exact test, using SigmaStat statistical software (SPSS Inc, Chicago, Ill). Kaplan-Meier survival curves were generated, and log-rank tests analyses of the statistical significance of variations between them were carried out using Statistical for Windows software (StatSoft Inc, Tulsa, Okla).

Adenoid cystic carcinoma is a rare and elusive cancer characterized by a protracted natural history; despite improvements in locoregional disease control, distant metastases can cause death 1 or even 2 decades after definitive treatment. Pathognomonic of the local growth of ACC is its insidious and widespread dissemination through submucosal and fibrous tissue planes around the primary site and its perineural extension through minor and major nerves. Distant metastases, when affecting the lung, are usually slow growing, sometimes apparently isolated, and frequently surgically resectable. When metastatic disease spreads to the bones, the course is frequently rapidly fatal.

Efforts to unearth reliable prognostic factors in this disease have dominated the ACC literature for the last decade. Interstudy agreement regarding the key prognostic factors has not been universal. Negative clinical prognosticators identified in previous studies include tumor site within minor salivary glands, infiltrative pattern of local growth and spread, increasing size and stage of tumor, predominantly solid histological features, presence of cervical metastases, positive margins at surgery, and perineural invasion, among others. In this review, we evaluated the prognostic implications of tumor site, histological features, cervical metastases, margin status, and perineural invasion. We identified solid histological features, major perineural invasion, and nodal positivity as predictors.

COMMENT

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of increased mortality. We also found that 4 or more presenting symptoms were negative prognosticators. In previous ACC studies from our institution, researchers have found negative prognostic impact from tumor size greater than 4 cm, clinical stage higher than II,11 and invasion of major (named) nerves.12 Garden et al12 found that positive margins did not influence survival, and this finding was corroborated by our data. Similarly, we confirmed an earlier finding that perineural invasion by ACC is a negative survival predictor, as well as a predictor of treatment failure when a major nerve is involved.12

Perineural invasion of major nerves, positive margins, and solid histological features were predictive of treatment failure in our patients. None of these factors was predictive of isolated locoregional recurrence; they became significantly predictive only when distant failure was included in the analysis. This failure to find predictors of locoregional treatment failure may stem from the low number of patients (n=13) in whom isolated locoregional failures occurred.

Figure 2 shows survival curves for patients with isolated locoregional recurrence and patients with isolated distant metastases. The figure clearly indicates that distant metastases cause the earliest mortality in ACC; in addition, the curve for isolated distant metastases reveals that locoregional control in ACC is no guarantee of prolonged survival. It may be that some factors leading to distant failure and some leading to locoregional failure travel independent pathways in ACC, and that current treatment modalities address mostly locoregional failure pathways, while distant disease pathways remain open. Consistent therapeutic closure of distant failure pathways likely awaits the advent of effective chemotherapeutic agents in this disease.

Clinical experience at our institution suggests that 2 populations of patients with ACC may exist—one doomed to rapid death from aggressive tumor, with survival measured in months to years, and one saddled with indolent disease, with sporadic recurrences and survival measured in decades. If these 2 populations truly exist, identification of factors placing patients in each group would be highly advantageous for patient counseling and therapeutic planning. Solid histological features certainly deserve suspicion as a key factor for the “aggressive” group, as does the presence of bone metastases. Several additional factors are undoubtedly at play.
tumor site, patients with primary tumors in the paranasal sinuses suffered more moderate to severe morbidity than did patients with primary tumors at other sites. The increased morbidity derives, in most cases, from sequelae of radiation therapy to the central face; specifically, the effect of radiation on the eyes, the central nervous system, and the pituitary gland.17,18

Most patients with ACC of the head and neck can achieve long-term survival, although many eventually die of disease at distant sites. Our disease-specific survival figures at 10 years (67.4%) and 15 years (39.6%) compare favorably with those in the bulk of the ACC literature. Our locoregional control rate of 85% bolsters our conviction that cure of head and neck disease is attainable in most patients. Early experience at our institution by Guillamondegui et al19 revealed a 50% crude local failure rate for parotid ACC treated with surgery alone; these results led to formulation of a combined-therapy policy for all but the smallest of low-grade ACC tumors with negative margins and no perineural spread. McNaney et al20 later showed 93% local control of tumors originating in the parotid with postoperative irradiation. Other researchers21–23 have concurred with the value of combined therapy in ACC.

In most cases, combined-modality therapy is essential for achieving prolonged disease control; furthermore, appropriately aggressive surgery with attainment of negative tissue margins is the linchpin of successful combined therapy. Total gross tumor removal should always be attempted; microscopic disease at resection margins should be pursued judiciously at the time of surgery.

Paranasal sinus tumors and combined-modality therapy are associated with increased morbidity. Treatment-related morbidity can be minimized through modern radiotherapeutic planning and execution, patient education, preventive measures (eg, use of sialogogues, fluoride treatment, temporomandibular joint therapy, care of the irradiated ear, and external auditory canal), and prompt, vigorous attention to complications.

Major perineural invasion, positive margins, and solid histological features predict treatment failures, while nodal metastases, major nerve invasion, solid histological features, and multiple presenting symptoms negatively affect survival. While treatment failure remains problematic for patients with ACC, particularly at distant sites, many recurrences can be treated, and prolonged survival with disease is common. Surgical resection may be considered for isolated pulmonary metastases, although no survival benefit has yet been demonstrated. Prolonged follow-up is essential for early detection and management of delayed complications or metastases. To maximize the survival of patients with ACC, perseverance and diligence are essential.

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